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Citation for published version (APA):

Straathof, N. J. W., Cramer, S. E., Hessel, V., & Noël, T. (2016). Practical photocatalytic trifluoromethylation and hydrotrifluoromethylation of styrenes in batch and flow. *Angewandte Chemie - International Edition*, 55(50), 15549-15553. <https://doi.org/10.1002/anie.201608297>

DOI:

[10.1002/anie.201608297](https://doi.org/10.1002/anie.201608297)

Document status and date:

Published: 01/01/2016

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Photoredox Catalysis

International Edition: DOI: 10.1002/anie.201608297
German Edition: DOI: 10.1002/ange.201608297

Practical Photocatalytic Trifluoromethylation and Hydrotrifluoromethylation of Styrenes in Batch and Flow

Natan J. W. Straathof, Sten E. Cramer, Volker Hessel, and Timothy Noël*

Abstract: Styrenes represent a challenging class of substrates for current radical trifluoromethylation and hydrotrifluoromethylation methods due to a myriad of potential side reactions. Herein, we describe the development of mild, selective and broadly applicable photocatalytic trifluoromethylation and hydrotrifluoromethylation protocols for these challenging substrates. The methods use *fac*-Ir(ppy)₃, visible light and inexpensive CF₃I and can be applied to a diverse set of vinylarene substrates. The use of continuous-flow photochemical reaction conditions allowed to reduce the reaction time and increase the reaction selectivity.

Olefins are versatile synthons for the synthesis of various commodity chemicals. Consequently, numerous catalytic methodologies have been developed allowing olefins to engage into efficient carbon–carbon or carbon–heteroatom bond forming reactions, such as, hydroformylations,^[1] hydroaminations^[2] and Wacker oxidations.^[3] One specific example that received a lot of attention in recent years is the trifluoromethylation and hydrotrifluoromethylation of olefins.^[4] Trifluoromethylated compounds are important for the pharmaceutical, agrochemical and material industries as this substituent imparts important properties to a molecule, such as improved bioavailability, lipophilicity and metabolic stability.^[5]

While several examples on the trifluoromethylation of terminal olefins have been reported, a direct and practical route to C–H functionalization of these structures remains a challenging task and is often hampered by the need for prefunctionalized substrates (Figure 1A).^[6] In this context, radical trifluoromethylation^[7] and hydrotrifluoromethylation^[8] strategies arose as efficient strategies to circumvent the need for olefin prefunctionalization.^[9] Despite the great progress, styrene derivatives remain an unsolved case due to the unique challenges with regard to unproductive polymerization, product isomerization, oxidation,^[10] dimerization^[11] and nucleophilic trapping (Figure 1B).^[12] Therefore, a key aspect in the development of new synthetic methods is the efficient single electron oxidation of the benzylic radical to suppress these undesired outcomes (Figure 1B). For example,

Figure 1. A) Reported protocols suffer from several disadvantages. B) Outline synthetic strategy to access trifluoromethylated and hydrotrifluoromethylated styrenes via photoredox catalysis and overview of the common pitfalls. C) Our strategy for the photocatalytic radical trifluoromethylation and hydrotrifluoromethylation of styrenes.

Qing et al. achieved a good selectivity for the desired trifluoromethylated styrene compounds but required the presence of electron-donating groups on the *ortho* position to prevent a nucleophilic attack on the carbocation.^[13] A versatile hydrotrifluoromethylation protocol for β -substituted styrenes was developed by Nicewicz et al., but terminal styrenes proved challenging due to their propensity for undesired polymerization.^[14] Nonetheless, a reliable and broadly applicable strategy to access these seemingly simple compounds remains underdeveloped but is highly desirable.

Herein, we report a facile method for both trifluoromethylation and hydrotrifluoromethylation of terminal and α - or β -substituted styrenes via visible light photoredox catalysis using CF₃I as an inexpensive trifluoromethylation reagent (Figure 1C). The method is mild (room temperature, visible light, use of weak bases) and displays a broad substrate scope.

[*] N. J. W. Straathof, S. E. Cramer, Prof. Dr. V. Hessel, Dr. T. Noël
Department of Chemical Engineering and Chemistry, Micro Flow
Chemistry & Process Technology
Eindhoven University of Technology
Den Dolech 2, 5612 AZ Eindhoven (The Netherlands)
E-mail: t.noel@tue.nl
Homepage: <http://www.NoelResearchGroup.com>

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201608297>.

In addition, continuous-flow photochemistry allowed to accelerate the trifluoromethylation protocol and to increase the *E/Z* ratio of trifluoromethylated styrenes.

Our efforts to effect the targeted trifluoromethylation of styrene (**1**) were initially focused on the use of Ru(bpy)₃Cl₂ as a common photocatalyst^[15] with CF₃I as cheap and abundant trifluoromethylating agent. Various bases and solvents were screened but no product could be obtained with this photocatalyst (see the Supporting Information). Next, *fac*-Ir(ppy)₃ was evaluated for this transformation (Table 1), as this

Table 1: Reaction discovery and optimization studies for the photocatalytic trifluoromethylation of styrene.^[a]

Entry	Base/Solvent	Yield ^[b]	<i>E/Z</i> ^[b]
1	DBU/CH ₃ CN	Trace	—
2	TMEDA/CH ₃ CN	Trace	—
3	DBU/DMF	Trace	—
4	K ₂ CO ₃ /DMF	3 %, (35 % after 72 h)	—
5	Cs ₂ CO ₃ /DMF	5 %, (57 % after 72 h)	—
6	KOAc/DMF	76 %	55:45
7	CsOAc/DMF	89 % (75 %)^[c]	74:26
Entry	Change from best conditions (entry 7)	Yield	<i>E/Z</i> ^[c]
8	No light	0 %	—
9	No photocatalyst	0 %	—
10	No base	Trace	—

[a] Reaction conditions: *fac*-Ir(ppy)₃ (1 mol %), styrene (0.5 mmol), base (1.5 mmol), solvent (5 mL, 0.1 M), visible light (2 × 24 W CFL), room temperature, stirred for 18 hours. [b] Yield and *E/Z* values are determined with ¹⁹F-NMR with α,α,α-trifluorotoluene as internal standard. [c] Volatile compound.

photocatalyst exhibits a higher reducing power in its excited state ($E_{1/2}^{\text{red}}[*\text{Ir}^{3+}/\text{Ir}^{4+}] = -1.72$ V vs. SCE, compared to $E_{1/2}^{\text{red}}[*\text{Ru}^{2+}/\text{Ru}^{3+}] = -0.81$ V vs. SCE). As proven by a Stern–Volmer kinetic analysis, this is sufficient to allow for oxidative quenching of the excited state of the photocatalyst by CF₃I ($E_{1/2} = -1.22$ V vs. SCE in DMF).^[16] The high quenching rate ($k_q = 8.7 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, with $\tau_0 = 1900$ ns, resulting in a quenching fraction of $Q > 0.95$) reveals that the required CF₃ radicals for the intended transformation can be efficiently generated. No product could be obtained in the presence of amine bases, presumably by reductive quenching of the excited state thus hampering the CF₃ radical formation process (Table 1, entries 1–3). However, switching to mild inorganic bases, which are not competent to quench the excited state of the photocatalyst, resulted in the formation of the targeted compound (Table 1, entries 4–7). Optimal results were obtained by using CsOAc in DMF furnishing the trifluoromethylated styrene in good yield (89 % ¹⁹F-NMR yield, 75 % isolated yield) within 18 hours (Table 1, entry 7). Control experiments established the importance of the photocatalyst, the presence of visible light and a suitable base as no reaction was observed in the absence of any of these (Table 1, entries 8–10).

Having found optimal reaction conditions, we set out to examine the scope of the photocatalytic trifluoromethylation of styrenes in batch (Scheme 1). Our protocol was found to readily accommodate a variety of styrenes (**1-A–5-A**). In addition, the presence of chlorine or bromine substituents were well tolerated providing opportunities for further decoration of the molecule (**6-A–8-A**). Also ester- and aldehyde-bearing derivatives were also well tolerated (**9-A–10-A**). Furthermore, a variety of challenging vinylic heterocycles, including pyridines, a pyrazine, and a thiazole, could be exposed to the reaction conditions giving access to the targeted trifluoromethylated compounds in satisfying yields (**11-A–14-A**). More complex substrates, such as estrone-derivative **15-A** and silane **16-A**, could be efficiently trifluoromethylated, highlighting the applicability of the described methodology for the synthesis of compounds of interest to the pharmaceutical and materials industry. Also α/β-disubstituted styrenes proved to be a suitable substrate class (**17-A–22-A**). Both β-methyl and α-methyl styrene could be efficiently trifluoromethylated (**17-A–18-A**). Other β-substituted styrenes gave predominantly the *E* isomer in good to excellent yields (**19-A–22-A**).

Despite the high yield for the desired compounds, the *E/Z* ratio was often poor in batch. We hypothesized that the thermodynamically most stable *E*-isomer was first formed and subsequently transformed into the *Z*-isomer via an energy transfer (ET) mechanism.^[17] During the course of our investigations, we observed that indeed the *E/Z* ratio was reduced at longer reaction times (see the Supporting Information). In order to obtain full conversion with a high *E/Z* ratio at short reaction times, the photocatalytic trifluoromethylation of styrenes was carried out in a continuous-flow photomicroreactor.^[18] Such flow reactors are ideally suited to carry out photochemical transformations^[19] as they provide homogeneous irradiation of the reaction mixture and facile scale-up via numbering up.^[20] The reaction could be completed in flow in less than an hour and the formation of the *Z* isomer could be avoided resulting in excellent *E/Z* ratios for **1-A** (see the Supporting Information). These observations appeared to be generally true (Scheme 1). A significant acceleration and a higher yield was observed when the reaction was carried out in a photomicroreactor resulting in a reduction of the reaction time (from 24–72 h in batch to 0.5–1.5 h in flow). Notably, higher *E/Z* ratios were observed in all cases which can be attributed to the significantly reduced reaction time, thus avoiding the occurrence of isomerization via an ET mechanism (see Supporting Information).

Next, we turned our attention to develop a suitable photocatalytic protocol for the hydrotrifluoromethylation of styrenes. During the initial screening of our trifluoromethylation protocol, we observed that in ethanol, along with 41 % of **1-A**, 12 % of the hydrotrifluoromethylated product was formed (Table 2, entry 1). An increase in yield was observed when dichloroethane/ethanol (9:1) was used as a solvent mixture (Table 2, entries 2 and 3). However, the product came along with many by-products, originating from for example, overoxidation and dimerization reactions. Screening of a small library of thiols and other H-atom donors revealed that the addition of aromatic thiols resulted in a clean

Scheme 1. Substrate scope for the photocatalytic trifluoromethylation of styrenes: 1) Batch reaction conditions: *fac*-Ir(ppy)₃ (0.5 mol %), styrene (0.5 mmol), CF₃I (0.8–1.5 mmol), CsOAc (1.5 mmol), DMF (5 mL, 0.1 M), visible light (2×24 W CFL), room temperature, stirred for 24 hours. 2) Continuous-flow reaction conditions: *fac*-Ir(ppy)₃ (0.5 mol %), styrene (0.5 mmol), CF₃I (0.8–1.5 mmol), CsOAc (1.5 mmol), DMF/MeOH (4.5 mL/0.5 mL, 0.1 M), visible light (3.12 W blue LED), room temperature. The residence time to reach full conversion is given for each compound. 3) Reported yields are those of isolated compounds. The E/Z ratio was determined with ¹⁹F-NMR. [a] Reaction time of 48 hours. [b] Combined yield of protected (60%) and unprotected (35%) compound. [c] Reaction time of 72 hours. [d] DMF/MeOH (4.5 mL/0.5 mL) used as a solvent system. [e] DMF/MeOH (4.0 mL/1.0 mL) used as a solvent system. [f] Large scale reaction in flow: 3.9 gram isolated product (see the Supporting Information).

Table 2: Reaction discovery and optimization studies for the photocatalytic hydrotrifluoromethylation of styrene.^[a]

Entry	Solvent	Aromatic thiol	Yield ^[b]
1	EtOH	—	12% ^[c,d]
2	CH ₂ Cl ₂ /EtOH (9:1)	—	25% ^[c]
3	Dichloroethane/EtOH (9:1)	—	27% ^[c]
4	Dichloroethane/EtOH (9:1)	Thiophenol (20 mol %)	13%
5	Dichloroethane/EtOH (9:1)	4-HTP (20 mol %)	23%
6	Dichloroethane/EtOH (9:1)	4-HTP (1.2 equiv)	94% (78%) ^[e]
Entry	Change from best conditions (entry 6)		Yield ^[b]
8	No light		0%
9	No photocatalyst		0%
10	No dichloroethane		55%

[a] Reaction conditions: *fac*-Ir(ppy)₃ (1 mol %), styrene (1.0 mmol), 4-HTP (1.2 mmol), dichloroethane/ethanol (18/2 mL, 0.05 M), visible light (2×24 W CFL), room temperature, stirred for 18 hours. [b] Yield are determined with ¹⁹F-NMR with α,α,α-trifluorotoluene as internal standard. [c] Complex and inseparable reaction mixture, incl. overoxidation, dimerization, etc. [d] Also, 41% of **1-A** was observed. [e] Isolated yield (volatile compound).

conversion of the starting material (see the supporting Information). Optimal results were obtained with 4-hydroxythiophenol (4-HTP) and increasing the amount to 1.2 equiv provided excellent yields (Table 2, entry 6). Control experi-

ments demonstrated that the reaction did not proceed in the absence of *fac*-Ir(ppy)₃ or light (Table 2, entries 8 and 9).

The optimized hydrotrifluoromethylation conditions proved generally useful to a wide variety of different styrenes (Scheme 2). High yields were obtained in most cases including 2-vinylnaphthalene (**3-B**), styrenes bearing aliphatic (**2-B**), hydroxy (**4-B**), acetyl-protected hydroxy (**5-B**) and halogen functional groups (**6-B–8-B**) and 4-vinylpyridine (**9-B**). Moreover, sterically more demanding substrates, such as α- and β-substituted styrenes, were efficiently hydrotrifluoro-

Scheme 2. Substrate scope for the photocatalytic hydrotrifluoromethylation of styrenes: Batch reaction conditions: *fac*-Ir(ppy)₃ (0.5 mol %), styrene (1.0 mmol), CF₃I (1.2 mmol), 4-HTP (1.2 mmol), dichloroethane/ethanol (18/2 mL, 0.05 M), visible light (2×24 W CFL), room temperature, stirred for 24 hours. Reported yields are those of isolated compounds.

methylated (**10-B–13-B**). Also for the hydrotrifluoromethylation protocol, continuous-flow photomicroreactors served as an enabling technology to reduce the reaction times of photocatalytic transformations (from 18 h in batch to 50 min in flow).

The products obtained by our trifluoromethylation and hydrotrifluoromethylation protocol serve as useful synthetic building blocks (Scheme 3A). As an example, we converted

Scheme 3. A) One-pot strategy combining photocatalytic trifluoromethylation/ cross-coupling of 4-ethynylphenyltrifluoroborate. B) Perfluoroalkylation and hydroperfluoroalkylation of styrene. For the reaction conditions, see the Supporting Information. Reported yields are those of isolated compounds. The *E/Z* ratio was determined with ^{19}F -NMR. [a] AcOH (1 mmol) was added to the reaction mixture, see the Supporting Information.

potassium 4-ethynylphenyltrifluoroborate according to our developed trifluoromethylation protocol. The corresponding trifluoromethylated organotrifluoroborate was subsequently subjected to C–C and C–N cross-coupling reaction conditions in a convenient one-pot protocol leading to products **23-A** and **24-A**, respectively.^[21] Notably, due to higher reaction temperatures, the *E*-isomer was exclusively formed.

Lastly, we evaluated the breadth of the perfluoroalkyl halide coupling partner in our photocatalytic protocol (Scheme 3B). Efficient perfluoroalkylation of styrene could be achieved with 1,1,1-trifluoro-2-iodoethane (**1C**), perfluoropropyl iodide (**2C**), heptafluoro-2-iodopropane (**3C**) and perfluorohexyl iodide (**4C**) as commercially available coupling partners. Also efficient hydroperfluoroalkylation was possible with these reagents resulting in excellent yields (**1D** and **4D**). Having access to perfluoroalkyl analogues by merely changing the coupling partner represents a significant advantage over other protocols that use perfluoroalkyl electrophilic reagents which are either expensive, not commercially available or difficult to synthesize.

In summary, we have established a robust methodology for the trifluoromethylation and hydrotrifluoromethylation of styrenes. Challenges associated with this substrate class were efficiently overcome by using visible light photoredox catalysis. The mild nature of the reaction conditions has been exemplified by the broad substrate scope (28 examples trifluoromethylation and 15 examples hydrotrifluoromethylation). A substantial reduction in reaction time and a higher *E/Z* selectivity for the trifluoromethylation process was witnessed under continuous-flow photochemical conditions. Other perfluoroalkyl halide coupling partners can be readily engaged in these reaction protocols giving rise to perfluoroalkylated analogues. Extending this chemistry to other challenging olefinic substrate classes is currently being explored in our laboratory.

Acknowledgements

Financial support for this work was provided by a VIDI grant (T.N., SensPhotoFlow, No. 14150) and a Marie Curie CIG grant (T.N., Grant No. 333659). Also funding by the Advanced European Research Council Grant (Grant number: 267443 for V.H.) is kindly acknowledged. We would like to thank Koen P. L. Kuipers (TU/e) for help with Stern–Volmer kinetics.

Keywords: continuous flow · hydrotrifluoromethylation · microreactor · photoredox catalysis · trifluoromethylation

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 15549–15553
Angew. Chem. **2016**, *128*, 15778–15782

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Manuscript received: August 25, 2016

Revised: October 25, 2016

Final Article published: November 15, 2016